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Changes in current-source density of interictal spikes in benign epilepsy of childhood with centrotemporal spikes following treatment with oxcarbazepine

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ABSTRACT

Purpose: The aim of this study was to detect clinical variables associated with the extent of change of the irritative zone in benign epilepsy of childhood with centrotemporal spikes (BECTS) after oxcarbazepine monotherapy.
Method: BECTS patients receiving oxcarbazepine monotherapy were retrospectively reviewed. Changes in current-source density (CSD) of the maximum negative points of interictal spikes prior to the start of oxcarbazepine treatment were compared with CSD following oxcarbazepine treatment for 6–12 months. CSD was measured using low-resolution brain electromagnetic tomography (LORETA). Patients were divided into two groups based on the change in CSD: increased-extent or decreased-extent. Comparisons were made between the groups based on the age of onset, seizure frequency before treatment, time interval between seizure onset and treatment start, time interval between the two EEGs, oxcarbazepine dosage at the follow-up electroencephalography, occurrence of daytime seizures, and seizure control.
Results: Fourteen patients were enrolled. Seven patients were in the decreased-extent group and six in the increased-extent group; one patient was excluded because she did not demonstrate any change in CSD. We found that seizure control differed significantly between the two groups: seizures were well-controlled in six out of seven patients in the decreased-extent group (85.7%), but in only one of six patients (16.7%) in the increased-extent group ($p = 0.03$). The other variables did not differ between the groups.
Conclusion: Seizure control may be associated with the extent of changes in the neuronal irritative zones of BECTS patients. We suggest that changes of CSD extent may be used as an imaging modality to evaluate clinical improvement in BECTS patients.

1. Introduction

Benign epilepsy of childhood with centrotemporal spikes (BECTS) is the most common idiopathic childhood focal epilepsy.[1] Morphologically similar centrotemporal spikes may be observed in various other clinical syndromes,[2] but the electroencephalographic (EEG) finding of centrotemporal spikes plays a decisive role in the diagnosis of BECTS in children with normal neurodevelopment.[3] Centrotemporal spikes are characterized by focal surface negative spikes with relatively prolonged duration, high amplitude, and bluntness.[4] These spike characteristics suggest that BECTS are generated by an extensive neuronal pool[4] and possesses relatively low epileptogenicity.[5]

Although the interictal spikes in BECTS have distinctive neurophysiological characteristics, the relationship between these discharges and the degree of seizure-control in a particular patient has yet to be clarified.[4] Furthermore, no correlation has been noted between the intensity of spike discharges in the EEG and the frequency, length, or duration of clinical seizures; or between an atypical morphology of interictal spikes and seizure frequency in previous studies.[6–8] In particular, the persistence of EEG abnormalities long after clinical seizure remission and extreme discrepancies characterized by very rare seizures on the one hand but high EEG activity on the other common. Clinical

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experience suggests that the EEG often remains relatively unchanged even after treatment has effectively stopped seizures.[1,9] These findings suggest that it is difficult to anticipate the clinical manifestations of BECTS based on the visual characteristics of interictal spikes. Having said that, a computer-based assessment[10] of interictal spikes in childhood partial seizures, including BECTS, demonstrated that the achievement of seizure control using antiepileptic medication is associated with changes in epileptic spike configuration, including decreases in spike amplitude and duration. The authors hypothesized that such changes in spike morphology may be caused by critical reductions in the epileptogenic neuronal pool, however they did not have the proper instruments to demonstrate this.[10]

Since that study was published, remarkable advances in functional imaging techniques have been made, and researchers now have the ability to observe neuronal activity and obtain 3-dimensional data in a non-invasive manner, for instance by using EEG current-source analysis. Low-resolution brain electromagnetic tomography (LORETA) is one of these functional imaging methods. It uses EEG measurements based on electrophysiological and neuroanatomical constraints.[11] LORETA can demonstrate 3-dimensional distributions of electrical neuronal activity, with maximum similarities of orientation and strength between neighboring neuronal populations.[11] Therefore, it may be an excellent tool for investigating the epileptogenic neuronal pools that correspond to interictal epileptic abnormalities. To date there are only few studies investigating the electrophysiological characteristics of BECTS using current-source analyses of EEG, and a current-source analysis using LORETA may be helpful for investigating the relationship between current-source changes of interictal spikes and seizure control. Thus, the purpose of this study was to investigate the relationship between distributional changes in irritative neuronal areas and seizure control in BECTS patients. A number of clinical factors were also analyzed to evaluate whether these factors are influenced by the extent of change in the irritative area following treatment.

2. Methods

2.1. Subjects

Children, newly diagnosed with epilepsy, who met the diagnostic criteria for BECTS, were recruited retrospectively from January 2009 to August 2013 at Gyeongsang National University Hospital. The diagnosis of BECTS was based on the following criteria: seizure onset between the ages of 4 and 14 years, blunt high-voltage centro-temporal or mid-temporal spikes or sharp-wave focus on EEG scans, a normal neurological examination, the absence of brain lesions and compatible seizure semiology. Of the newly diagnosed BECTS patients, only those who had undergone at least two EEG recordings were included in the study: the first EEG immediately following the diagnosis of BECTS and the start of oxcarbazepine (OXC) monotherapy (baseline) and the second EEG during the maintenance phase of treatment, 6–12 months after drug initiation (post-treatment). To minimize the effect associated with the use of different antiepileptic drugs (AED), only BECTS patients undergoing OXC monotherapy were included. Patients were excluded if (1) there was inadequate data, or they were unavailable for follow-up, (2) they experienced breakthrough seizures due to low compliance with OXC, (3) they were receiving polytherapy or taking AEDs other than OXC, or (4) they had an inadequate EEG follow-up interval.

During the study period, a total of 28 patients were newly diagnosed with BECTS. Within this group, 14 patients were excluded for different reasons (1) unavailability for follow-up ($n = 4$); (2) breakthrough seizures due to poor compliance with OXC treatment ($n = 3$); (3) polytherapy or AED medication other than OXC ($n = 3$); and (4) inadequate EEG follow-up interval ($n = 4$). Ultimately, 14 patients were enrolled in the study.

2.2. EEG recording

EEG recordings were taken for a minimum of 30 min in each patient, with the majority of recordings obtained during the waking state. A 32-channel digital EEG machine (Comet® EEG machine; Grass-Telefactor; West Warwick, Rhode Island, USA) was used in conjunction with 25 electrodes placed on the scalp according to the International 10-20 System (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, F9, F10, T9, T10, P9, P10, Fz, Cz, and Pz). The sampling rate was 400 Hz, and two EEGs from each patient were analyzed.

2.3. EEG analysis using LORETA

Brain Electrical Source Analysis (BESA; V. 5.1; MEGIS; Grafelfing, Germany) software was used to select epochs for data processing. After the visual selection of typical interictal spikes, 20 EEG segments of 1 s epochs, including 500 ms before and 500 ms after the maximum positive point of the spikes, were obtained. These 20 epochs were averaged to one spike for each set of EEG data in each patient. Thus, one averaged spike was obtained from the baseline EEG, and another was obtained from the post-treatment EEG for each patient.

Two LORETA images corresponding to the positive peak of the averaged spikes were obtained from each patient to identify the anatomical distribution and extent of the current source of the averaged spikes. LORETA is a distributed model that adapts a depth weighting to compensate for the drawbacks of the minimal norm approach.[11,12] The area with the highest current density is the location of current source.[13] To objectively define the distribution of the current source, percentiles were used to determine the threshold of significance. Because the probability distribution for the current source suggested that the 95th percentile would be reasonable, a current-source distribution over the 95th percentile was considered the threshold of significance.[14] Therefore, we calculated a LORETA value of mean +2 standard deviations among all LORETA values in each EEG, and considered this the threshold value of LORETA images in each EEG. The neuronal cortex has been modeled as a collection of volume elements (voxels) in the digitized Talairach atlas (provided by the Brain Imaging Center, Montreal Neurological Institute), and LORETA represents a total of 2394 voxels at 7-mm spatial resolution.[11] For quantitative analysis, the voxels for the current-source density (CSD) of the averaged spikes of the baseline and post-treatment EEGs were enumerated and compared. The complete EEG data were analyzed by an investigator (SJ). The investigator who undertook the LORETA analysis did not have access to any clinical information regarding the patients during the entire analytic process.

2.4. Acquisition of clinical information and statistical analysis

Clinical data were acquired by means of a chart review and parental documentation. Clinical factors included age of onset, seizure frequency before treatment, time interval between seizure onset and treatment start, time interval between the two EEGs, AED dosage at the follow-up EEG, and seizure control. Seizure occurrence was measured according to parental documentation, and seizure frequency at baseline was defined as seizure number per month. Patients were categorized as "well-controlled" if they had been seizure-free during the time interval between the baseline and post-treatment EEGs (at least six months), and as "poorly-controlled" if they had experienced a recurrence of a seizure or seizures during the same time interval.

The patients were divided into two groups according to the extent of change in the voxels of CSD between the two EEGs: increased extent and decreased extent. One patient was not included in the factor analysis because there was no change in CSD between the baseline and post-treatment EEGs. The clinical variables mentioned above were then compared between the two groups using a Mann–Whitney *U*-test for numerical data and a Fisher's exact test for categorical data. A *p*-value less than 0.05 was considered statistically significant. All analyses were performed using SPSS for Windows version 12.0 (Chicago, IL, USA).

3. Results

3.1. Conventional EEG inspection and current-source analysis

For all patients, the interictal spikes exhibited a centrotemporal, mid-temporal, or mid-parietal predominance in the right or left cerebral hemisphere. The CSD of the averaged spikes were distributed among the middle frontal gyrus, postcentral gyrus, superior-middle-inferior temporal gyri, insula, fusiform gyrus, cingulate gyrus, and inferior parietal lobule (Table 1). The primary CSD regions did not change in any of the patients following OXC medication, although the extent of the change in CSD differed between the two sequential EEGs for all patients except Patient 12. Following the administration of OXC, the number of CSD voxels decreased in seven patients, increased in six patients, and remained unchanged in one patient (Table 1). For example, in Patient 4, the maximal points of CSD were at the superior temporal gyrus and the middle temporal gyrus of the left hemisphere in the baseline EEG and at the postcentral gyrus of the same hemisphere in the follow-up EEG; the number of CSD voxels decreased from 143 to 107 (Fig. 1). In Patient 14, the maximal points of CSD were at the inferior frontal gyrus, middle temporal gyrus, postcentral gyrus, and insula of the left hemisphere in the baseline EEG and at the middle frontal gyrus, middle temporal gyrus, and cuneus of the same hemisphere in the follow-up EEG; the number of CSD voxels increased from 108 to 124 (Fig. 2).

3.2. Factors associated with the distributional changes in CSD

Seizure control was significantly different between the increased-extent group and the decreased-extent group ($p = 0.03$). Seizures were well-controlled in six patients in the decreased-extent group (85.7%) but in only one patient (16.7%) in the increased-extent group (Table 2). The number of CSD voxels remained unchanged in one patient, who exhibited a poor clinical course; this patient was excluded from the factor analysis. The age of onset, gender distribution, interval between the two EEGs, baseline seizure frequency, interval between seizure onset and medication start, occurrence of daytime seizures, and OXC dosage at the time of the follow-up EEG were not significantly different between the two groups.

Table 2
Comparison of clinical factors between the increased-extent group and the decreased-extent CSD group.

	Decreased-extent CSD group ($n = 7$)	Increased-extent CSD group ($n = 6$)	p[a]
Age (years)			
Onset[b]	9.28 ± 1.70	7.67 ± 2.12	0.18
1st EEG[c]	9.71 ± 2.06	8.17 ± 2.50	0.30
2nd EEG[d]	10.60 ± 1.90	9.17 ± 2.50	0.30
Number of females (%)	6 (85.7%)	3 (50.0%)	0.30
Interval between the two EEGs (months)	10.43 ± 2.07	11.12 ± 1.33	0.63
Baseline seizure frequency (per month)	1.54 ± 1.05	1.98 ± 1.52	0.37
Time interval from Sz onset to treatment (month)	5.00 ± 3.91	7.00 ± 4.56	0.45
OXC dosage at the follow-up EEG (mg/Kg)	13.57 ± 4.76	18.33 ± 5.16	0.14
Number of patients with good seizure control (%)	6 (85.7%)	1 (16.7%)	0.03

CSD: current source density, EEG: electroencephalography, Sz: seizure, OXC: oxcarbazepine.
[a] Mann–Whitney *U*-test or Fisher's exact test.
[b] Age at onset of seizures.
[c] Age at baseline-EEG performed.
[d] Age at post-treatment EEG performed.

4. Discussion

The primary finding of the present study was that the distribution of CSD of interictal spikes in BECTS patients tended to decrease when seizures were controlled by OXC. These findings also suggest that seizure control may be associated with the extent of changes in the neuronal irritative zones of BECTS patients. The

Table 1
Extent of changes in the current-source density of interictal spikes and the seizure control status following oxcarbazepine treatment in patients with benign epilepsy of childhood with centrotemporal spikes.

Patient no.	Age (year)			Gender	CSD (baseline)		CSD (after treatment)		Seizure control
	Onset[a]	1st EEG[b]	2nd EEG[c]		Maximal points	No. of voxels	Maximal points	No. of voxels	
1	10	11	12	F	MFG, PCeG, PCiG, insula (Rt)	126	MFG, PCeG, CG, cuneus (Rt)	119	Good
2	8	8	9	M	MTG, ITG (Lt)	150	STG, MTG (Lt)	168	Poor
3	5	5	6	F	STG, ACG, precuneus (Rt)	97	STG, ACG, IPL (Rt)	130	Poor
4	10	10	11	M	STG, MTG (Lt)	143	PCeG (Lt)	107	Good
5	6	7	8	M	PCeG, insula (Lt)	104	STG, IPL (Lt)	114	Poor
6	10	11	12	F	STG, IPL, ACG (Lt)	131	FG, IPL (Lt)	108	Poor
7	10	10	11	F	STG, MTG (Lt)	152	MTG, ACG (Lt)	138	Good
8	9	10	11	F	IFG, PCeG, insula (Rt)	104	MFG, STG, IPL (Rt)	118	Poor
9	11	12	12	F	IFG, precuneus (Rt)	136	PCeG (Rt)	107	Good
10	6	6	7	F	STG (Lt)	125	MTG (Lt)	118	Good
11	11	12	13	F	MFG, STG, IPL (Lt)	104	MTG, PCeG, CG (Lt)	123	Good
12	8	9	10	F	MTG, IPL (Lt)	149	MTG, IPL (Lt)	149	Poor
13	8	8	9	F	MFG, STG, PCeG, CG (Lt)	118	IFG, STG (Lt)	107	Good
14	7	7	8	M	IFG, MTG, PCeG, insula (Lt)	108	MFG, MTG, cuneus (Lt)	124	Poor

CSD: current source density, EEG: electroencephalography, F: female, M: male, Lt: left, Rt: right, MFG: middle frontal gyrus, PCeG: postcentral gyrus, PCiG: posterior cingulate gyrus, MTG: middle temporal gyrus, ITG: inferior temporal gyrus, STG: superior temporal gyrus, ACG: anterior cingulate gyrus, IPL: inferior parietal lobule, FG: fusiform gyrus, CG: cingulate gyrus.
[a] Age at onset of seizures.
[b] Age at baseline-EEG performed.
[c] Age at post-treatment EEG performed.

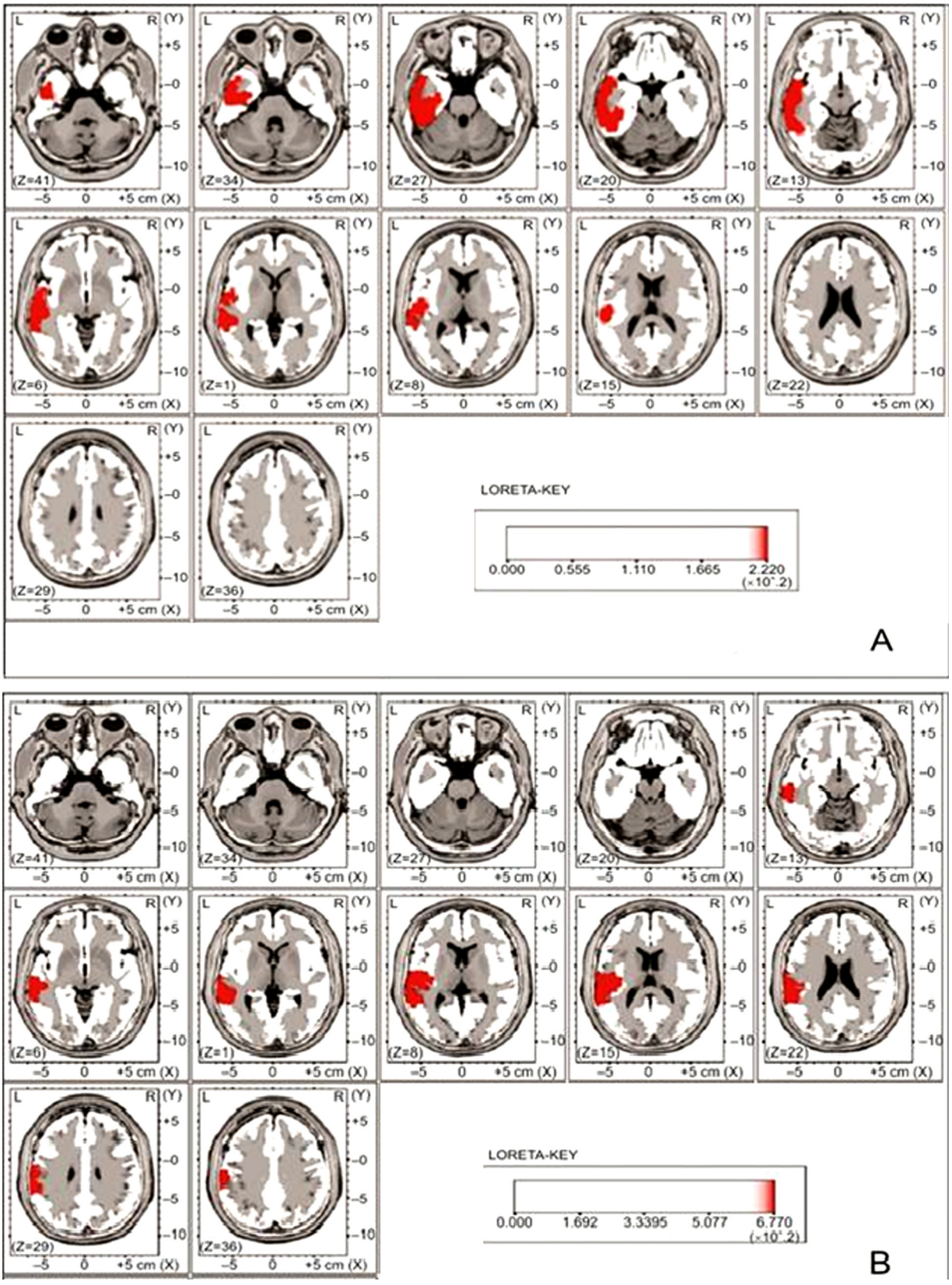

Fig. 1. Distribution and extent of change in current-source density (CSD) in a 10-year-old male patient (Patient 4). The maximal points of CSD were at the superior temporal gyrus and the middle temporal gyrus of the left hemisphere on the baseline EEG and at the postcentral gyrus of the same hemisphere on the follow-up EEG. The number of CSD voxels decreased from 143 to 107 from baseline to follow-up.

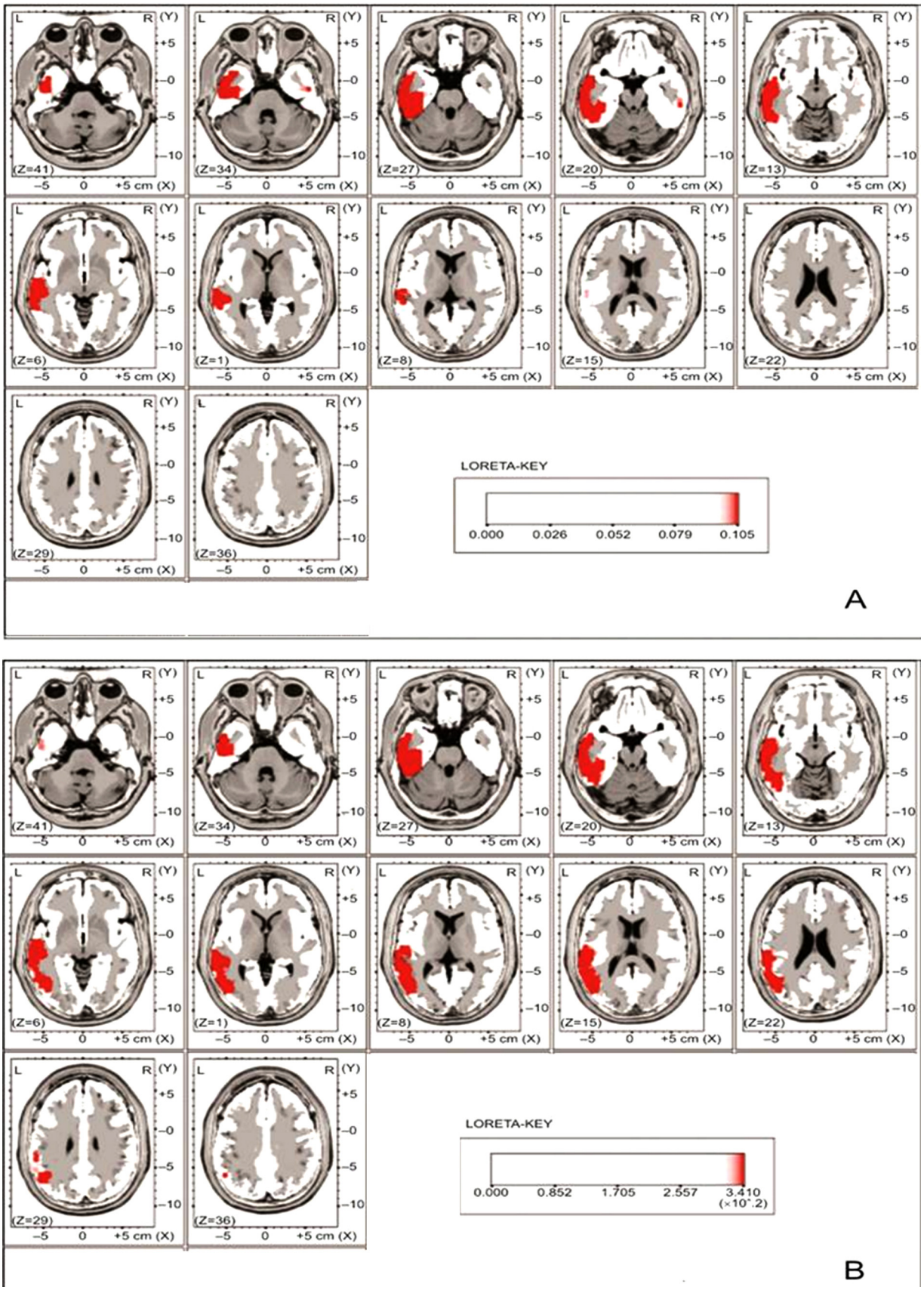

Fig. 2. Distribution and extent change of current-source density (CSD) in a 7-year-old male patient (Patient 14). The maximal points of CSD were at the inferior frontal gyrus, middle temporal gyrus, postcentral gyrus, and insula of the left hemisphere on the baseline EEG and the middle frontal gyrus, middle temporal gyrus, and cuneus of the same hemisphere on the follow-up EEG. The number of CSD voxels increased from 108 to 124 from baseline to follow-up.

irritative zone is the cortical area that generates interictal spikes, and is associated with the epileptogenic zone. The epileptogenic zone is a cortical area that would have to be resected or disconnected to obtain complete seizure control due to its association with the irritative zone as well as the seizure onset zone, any epileptogenic lesion, and the functional deficit zone. Although the irritative zone overlaps with the epileptogenic zone, the entirety of the irritative zone is not always included in the epileptogenic zone.[15] Therefore, the decrease in the spatial extent of the irritative zone after achievement of seizure control in this study cannot be considered direct evidence of a reduction of the epileptogenic zone in BECTS patients. However, the current results indicate that the extent of changes observed by LORETA imaging can be used as a biomarker of clinical improvement in BECTS patients.

It is generally accepted that the frequency and persistence of interictal spikes do not predict the severity and frequency of seizures or the prognosis of BECTS patients.[16] However, the extent of the changes in CSD of interictal spikes was associated with the clinical course of BECTS patients in this study. The pathophysiology underlying BECTS is thought to be a hereditary impairment of brain maturation in the lower Rolandic cortex.[17] A hyper-excitable Rolandic cortex tends to mature and stabilize with age.[17] The favorable clinical course of the decreased-extent group following the use of OXC in this study may reflect the progression of cortical maturation, which may in turn have decreased the extent of the cortical irritative zone in the patients. The reduced extent of CSD observed in this study may indicate a decrease in the area of the irritative zone in BECTS patients. On the other hand, an increase in the extent of the irritative zone suggests that the timing of maturation in the hyper-excitable cortex may inherently differ among individuals or may be actively disturbed in some individuals. The poor clinical course of the increased-extent group in this study may suggest that it is difficult to control seizures during an active period of cortical hyper-excitability.

Several studies have tested whether the extent of EEG abnormalities seen in BECTS patients represents a risk for multiple seizures or a reason for polytherapy, but the presence of bilateral epileptiform activity has not been found to be a risk factor.[7,18,19] Although these studies analyzed only the bilaterality of centro-temporal spikes, the findings support the concept that the characteristics of interictal spikes in BECTS patients do not predict their prognosis. A recent study,[20] however, did identify a possible relationship between EEG abnormalities and the prognosis of BECTS. In that study, patients with atypical benign partial epilepsy (ABPE) that evolved from BECTS exhibited extended periods of high-frequency spikes with a frontal focus.[20] The authors[20] suggested that the characteristics of these EEG abnormalities in ABPE patients may be associated with disturbances of brain maturation. By the same token, the increased extent of CSD observed in the EEG data from the current study may suggest disturbances in brain maturation and a risk for BECTS patients to develop ABPE. CSD analysis with sequential EEGs could be used to observe progression of brain maturation and predict the prognosis of BECTS patients.

Another question of interest is whether responsiveness to OXC influences the extent of changes in CSD and alters the course of the disease. Most AEDs seem to have little or no effect on interictal epileptiform discharges, regardless of their effectiveness in controlling seizures.[21] This suggests that the effectiveness of an AED against seizures is not related to its ability to suppress interictal epileptiform discharges.[22] However, Frost el al.[10] used a computer-based assessment of interictal spike morphology to demonstrate that AED medication could alter epileptic-spike configurations, and they found decreased amplitude and duration and increased sharpness of the spikes in BECTS patients. These changes were associated with pharmacological seizure control achieved by phenobarbital and carbamazepine. Based on these findings, the authors suggested that the changes in spike morphology were caused by a critical reduction in the epileptogenic neuronal pool that occurred due to effective drug action.[10] A recent study found an improvement, or normalization, of interictal epileptiform discharges and good seizure control in conjunction with the preservation of cognitive functioning following OXC monotherapy in children with BECTS.[23] These findings suggest that OXC may suppress or improve focal interictal epileptiform discharges in children with BECTS concomitant with effective seizure control. In addition to OXC, levetiracetam has also been shown to decrease interictal epileptiform discharges and to have a beneficial effect on language function in BECTS patients.[24]

The hypothesis of Frost et al. may apply to the present study based on the fact that OXC treatment led to a critical reduction in the epileptogenic neuronal pool,[10] which manifested as decreased CSD in patients with a good clinical course. However, it should be noted that Frost et al.[10] estimated spike configurations two weeks after AED administration with phenobarbital and carbamazepine, whereas the current patients were reassessed following 6–12 months of OXC therapy. It is possible that various factors, including the natural course of BECTS, affected the current findings during this interval. Considering the higher OXC dose given to the increased-extent group in this study, the extent of changes in CSD appear to be associated with an individual's maturation status with respect to cortical hyper-excitability, rather than with OXC itself. Therefore, the action of OXC does not appear to be directly related to the extent of changes in CSD. To clarify this issue, further investigation with a control group, such as BECTS patients without AED medication or with different AEDs, is necessary. Although the seizure control exerted by OXC may be one of the factors underlying the reduction in the cortical irritative zone in BECTS patients, various other factors that could not be investigated may also affect the natural course of this disease or the extent of changes in the cortical irritative zone.

This study has several strengths and limitations. To the best of our knowledge, the current study is the first attempt to analyze the CSD of interictal spikes using LORETA to show whether the extent of changes in the irritative zone is associated with the clinical characteristics of BECTS patients. The results of this study contributes to the debate concerning the relationship between interictal spike discharges and seizure control in BECTS. However, the sample size in the present study was too small to allow us to draw final conclusions. Furthermore, the current study design may not predict the clinical course or final prognosis of BECTS patients because the interval between the two EEGs and the overall clinical observation period may have been inadequate. Although the neuropsychological and language outcomes in BECTS patients are interesting and debatable issues, these functions were not assessed in this study. The potential for selection bias may be another limitation of this study because severe patients were excluded and we only included patients who maintained OXC monotherapy throughout the observation period. The majority of issues mentioned above are related to the retrospective format of this study. Therefore, further work with a prospective format, serial EEGs, a longer duration of clinical observation, and assessment of neuropsychology and language is necessary.

5. Conclusion

The present study provides preliminary evidence demonstrating a relationship between the clinical course and the extent of changes of the cortical irritative zone in children with BECTS. Distributed models of current-source analysis using EEG waveforms, including LORETA, can demonstrate the cortical irritative zones and may be helpful to better understand the electrophysiological characteristics

of children with BECTS and to predict the risk of frequent seizures and drug resistance.

Disclosure

The authors report no disclosures. We confirm that we have read the Journal's position on issues involved in ethical publication, and affirm that this report is consistent with those guidelines.

Conflict of interest

None of the authors have a conflict of interest to disclose.

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